From:	Kramer, George
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Subject:	teflubenzuron
Date:	Friday, March 13, 2015 1:33:55 PM
Attachments:	Bicyclopyrone Briefing Materials for ROCKS Meeting_AD071814.docx

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Hey BA,
Can you send a copy of the rat metabolism DER? I'll also need your section (Hazard Considerations) for the ROCKS summary Doc. See the attached file for an example.
Thanks!
GK

Bicyclopyrone: Briefing Materials for ROCKS Meeting

Team Proposal

The briefing package should begin with team proposal for residues of concern, along with a brief rationale.

Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression			
Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop		
	Rotational Crop		
Livestock	Ruminant		
	Poultry		
Drinking Water			Not Applicable

Rationale

The team should include a rationale for their proposal.

Physical/Chemical Characteristics

The following table, which is found in most residue chemistry DERs, should be included.

TABLE A.2. Physicochemical Properties of the [Technical Grade Test Compound: name of compound.] [Note: add rows as needed to accommodate multiple test compound]		
Parameter	Value	Reference
Melting point/range		
pH		
Density		
Water solubility (__°C)		
Solvent solubility (mg/L at __°C)		
Vapor pressure at __°C		
Dissociation constant (pK_a)		
Octanol/water partition coefficient Log(K_{OW})		
UV/visible absorption spectrum		

Residue Chemistry Considerations

The following table should be completed, preferably by the residue chemistry contractor when they are reviewing the plant and

livestock metabolism studies. Note that the lines for water and rat will need to be added at a later date, and are optional, but preferred. Metabolic pathways included in the DERs should be included in this section as well.

Table B.2. Tabular Summary of Metabolites and Degradates			
Chemical Name (other names in parenthesis) and Structure	Matrix	Percent TRR (PPM) [1]	
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)
Parent	Crop 1		
	Crop 2		
	Crop 3		
	Rotational Crops		
	Ruminant		
	Poultry		
	Rat		
	Water		
Degradate (*n*)	Crop 1		
	Crop 2		
	Crop 3		
	Rotational Crops		
	Ruminant		
	Poultry		
	Rat		
	Water		

The final row of the table should have a concise summary of relevant parameters.
Crop 1; MRID No.; Application Rate; Level of exaggeration compared to label rate; timing; pre-harvest interval.
Livestock 1; MRID No.; Feeding Level; Level of exaggeration compared to maximum dietary burden; days of dosing; pre-slaughter interval.
Rotational Crops; MRID No.; specific crops, Level of exaggeration compared to label rate; application type; range of plant-back intervals.
Rat 1; MRID No.; dosing level; other specific

Examples:
Apple, 12345678; 1 lb ai/A; 3X rate; petal fall; 90.
Lettuce, 12345678, 3 lb ai/A; 5x; immature leaves, 10 days.
Goats; 12345678; 10 ppm; 25X MTDB; 5 days; 12 hour PSI.
Rotational Crops; 12345678; 1x, applied to bare soil;30-120 day PBI
Rat Metabolism; 20 mg gavage dose; Sprague-Dawley, 1 day depuration.

The following table should be provided from the DER of each radiolabeled study (i.e., plant metabolism, livestock metabolism, and confined rotational crop, as applicable).

Table C.2.3.	**Summary of Characterization and Identification of Radioactive Residues in [Insert Matrix] Following Application of Radiolabeled [Chemical] at [Rate].** [Note: Modify the table and/or add tables as needed to accommodate the fractionation scheme, matrices analyzed, radiolabel positions, sample timing, and other aspects of the experimental design.]					
Compound	Matrix 1		Matrix 2		Matrix 3	
	TRRs = xx ppm		TRRs = xx ppm		TRRs = xx ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
[Parent]						
[Metabolite 1]						
[Metabolite 2]						
[Metabolite 3]						
[Metabolite 4]						
Total identified						
Total characterized						
Total extractable						
Unextractable (PES)[1]						
Accountability[2]						

[1] Residues remaining after exhaustive extractions.

TABLE C.4.	**Summary of Residue Data from Crop Field Trials with [chemical].**									
Commodity	Total Applic. Rate (lb a.i./A) (kg a.i./ha)	PHI (days)	Residue Levels (ppm)							
			n	Min.	Max.	HAFT*	Median (STMdR)	Mean (STMR)	Std. Dev.	
If there is more than one analyte in the study, specify it here. Residue summary for each analyte should be set off by a similar separator row specifying the analyte.										

* HAFT = Highest Average Field Trial.

Hazard Considerations

The toxicity profile table and acute toxicity table from Appendix A to the risk assessment should be provided. If endpoints have been selected, then the toxicity endpoint table should be provided. If the team has done a lit search on any of the metabolites, a summary of the results should be provided. Table 4 from the rat metabolism DERs (870.7485) which lists all of the identified metabolites should be included as well, along with any metabolic pathways from the DER.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4.1 Summary of Toxicological Doses and Endpoints for bicyclopyrone for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (General Population, including Infants and Children)	There were no effects up the highest dose tested in the Acute Neurotoxicity study, and there were no other studies appropriate for this exposure scenario. Thus no study will be chosen for this exposure scenario.			
Acute Dietary (Females 13-49 years of age)	NOAEL = 1 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Acute RfD = 0.01 mg/kg/day aPAD = 0.01 mg/kg/day	**Prenatal Developmental Study (Himalayan rabbits)** Developmental LOAEL = 10 mg/kg/day based on an increased number of skeletal variations (supernumerary ribs and slowed costal cartilage development).
Chronic Dietary (All Populations)	LOAEL= 0.28 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 10x (UF_L)	Chronic RfD = 0.0028 mg/kg/day cPAD = 0.00028 mg/kg/day	**Carcinogenicity (rat)** LOAEL = 0.28 mg/kg/day based on a dose dependent increase increased incidence of thyroid follicular hyperplasia in males, and an increased incidence of chronic progressive nephropathy in the kidneys of males.
Incidental Oral Short- (1-30 days) and Intermediate-Term (1-6 months)	NOAEL= 2.15 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Residential LOC for MOE = 100	**Reproduction and fertility effects (rat)** LOAEL = 43.65 mg/kg/day based upon decreased absolute body weights (decreases ≥ 10%)

Table 4.5.4.1 Summary of Toxicological Doses and Endpoints for bicyclopyrone for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- (1-30 days) and Intermediate-Term (1-6 months)	NOAEL = 1 mg/kg/day DAF= 20.44% [1]	UF_A= 10x UF_H=10x FQPA SF= 1x	Residential LOC for MOE = 100	**Prenatal Developmental Study (Himalayan rabbits)** Developmental LOAEL = 10 mg/kg/day based on an increased number of skeletal variations (supernumerary ribs and slowed costal cartilage development).
Inhalation Short- (1-30 days) and Intermediate-Term (1-6 months)	NOAEL = 1 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Residential LOC for MOE = 100	**Prenatal Developmental Study (Himalayan rabbits)** Developmental LOAEL = 10 mg/kg/day based on an increased number of skeletal variations (supernumerary ribs and slowed costal cartilage development).
Cancer (oral, dermal, inhalation)	**Classification:** *"Suggestive evidence of cancer."*			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable. [1] Dermal-absorption factor derived from MRID 47842239.

Table 4.5.4.2 Summary of Toxicological Doses and Endpoints for bicyclopyrone for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- (1-30 days) and Intermediate-Term (1-6 months)	NOAEL = 1 mg/kg/day DAF= 20.44% [1]	UF_A= 10x UF_H=10x	Occupational LOC for MOE = 100	**Prenatal Developmental Study (Himalayan rabbits)** Developmental LOAEL = 10 mg/kg/day based on an increased number of skeletal variations (supernumerary ribs and slowed costal cartilage development).
Inhalation Short- (1-30 days) and Intermediate-Term (1-6 months)	NOAEL = 1 mg/kg/day	UF_A= 10x UF_H=10x	Occupational LOC for MOE = 100	**Prenatal Developmental Study (Himalayan rabbits)** Developmental LOAEL = 10 mg/kg/day based on an increased number of skeletal variations (supernumerary ribs and slowed costal cartilage development).
Cancer (oral, dermal, inhalation)	**Classification:** *"Suggestive evidence of cancer."*			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study. [1] Dermal-absorption factor derived from MRID 47842239.

Table A.2.1. Acute Toxicity Profile - Bicyclopyrone

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral [rat]	47841966	LD_{50} females >5000 mg/kg bw (94.5% a.i.)	IV
870.1200	Acute dermal [rat]	47841967	LD_{50} (Combined) >5000 mg/kg (94.5% a.i.)	IV
870.1300	Acute inhalation [rat]	47841968	LC_{50} (Combined) >5.2 mg/L (94.5% a.i.)	IV
870.2400	Acute eye irritation [rabbit]	47841970	Based on the mean degree of eye irritation, no require classification.	IV
870.2500	Acute dermal irritation [rabbit]	47841969	No dermal irritation was observed.	IV
870.2600	Skin sensitization [mice]	47841971	Not dermal sensitization response in mice	-

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	14-Day oral toxicity (rat)	47841988 (2012) acceptable/non-guideline 0, 0.5 , 1, 2.5, 5 or 10 ppm	NOAEL = 10 ppm LOAEL was not observed
870.3150	28-Day oral toxicity (dog)	47841973 (2012) acceptable/non-guideline 0, 10, 100, and 250 mg/kg/day [M/F]	NOAEL = 100 mg/kg/day LOAEL = 250 mg/kg/day based upon clinical signs, bodyweight loss and reduced food consumption for one male on day 7. Various clinical pathology parameters were affected, and urine phenolic acid concentrations and plasma tyrosine and bicyclopyrone concentrations were elevated.
870.3100	90-Day oral toxicity (mouse)	47842172 (2012) acceptable/guideline 0, 100, 3500 and 7000 ppm (0, 15.4/20.8, 542.6/808.5, and 1127.4/1343.5 mg/kg/day [M/F])	NOAEL = 7000 ppm (1127.4/1343.5 mg/kg/day [M/F]) LOAEL was not observed .

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat)	47841975 (2012) acceptable/guideline 0, 2.5, 10, 2500, and 5000 ppm M: 0, 0.18/0.22, 0.72/0.88, 183.07/228.8, and 363.12/442.3 [M/F]) mg/kg/day	NOAEL = 0.72/0.88 mg/kg/day [M/F] LOAEL = 183.07/228.82 mg/kg/day based upon an increased incidence of eye opacity in both sexes, decreased absolute body weights and food consumption in males, and an increased incidence of ocular keratitis in both sexes.
870.3150	90-Day oral toxicity (dog)	47841976 (2012) acceptable/guideline 0, 5, 25, 125 mg/kg/day [M/F]	NOAEL = 125 mg/kg/day LOAEL was not observed.
870.3200	28-Day dermal toxicity (rat)	47841978 (2012) acceptable/guideline 0, 50, 250, 1000 mg/kg/day [M/F]	NOAEL = 50 mg/kg/day LOAEL = 250 mg/kg/day based on eye lesions (keratitis or degeneration of corneal epithelium) in a low number of animals. .

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700a	Prenatal developmental (rats)	47841993 (2012) acceptable/guideline 0, 100, 500, 1000 mg/kg/day [F]	**Maternal** NOAEL = 1000 mg/kg bw/day. The maternal LOAEL was not observed. **Developmental** NOAEL was not observed LOAEL = 100 mg/kg/day various skeletal variations
870.3700b	Prenatal developmental (New Zealand White rabbits)	47841996 (2012) acceptable/guideline 0, 10, 50, and 200 mg/kg/day [F]	**Maternal** NOAEL = 50 mg/kg/day LOAEL = 200 mg/kg/day based on mortality/moribundity in conjunction with minimal food consumption and effects on body weight changes. **Developmental** NOAEL was not observed LOAEL = 10 mg/kg/day based on skeletal variations (the appearance of 13th full rib, and the 27th presacral vertebrae).

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700b	Prenatal developmental (Himalayan rabbits)	47841998 (2012) acceptable/guideline 0, 10, 50, and 250 mg/kg/day [F]	**Maternal** NOAEL = 50 mg/kg/day LOAEL = 250 mg/kg/day based upon macroscopic findings in the stomach wall of females and an increased incidence of post-implantation loss. **Developmental** NOAEL was not established LOAEL = 10 mg/kg/day based upon a statistically significant increase in the foetal incidence of interventricular septum variations, an abnormal heart perimembraneous region (abnormal surface), and an increased incidence of unilateral missing kidney and ureters.
870.3700b	Prenatal developmental (Himalayan rabbits)	47841999 (2012) acceptable/guideline 0, 1, 10, 250 mg/kg/day [F]	**Maternal** NOAEL = 10 mg/kg/day LOAEL = 250 mg/kg/day based on 2 dams killed on day 22 post coitum due to general weak condition, decreased activity and prostrate position and at macroscopic examination had findings indicative of irritations in the stomach (red and dark red foci). **Developmental** NOAEL = 1 mg/kg/day LOAEL = 10 mg/kg/day based on an increased number of skeletal variations (supernumerary ribs and slowed costal cartilage development).

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3800	Reproduction and fertility effects (rat)	47842127 (2012) acceptable/guideline 0, 25, 500, and 5000 ppm 0, 2.15/2.65, 43.65/52.7, 435.5/534 mg/kg/day [M/F]	**Parental/Systemic** NOAEL was not established LOAEL = 2.15/2.65 (M/F) based upon ocular effects (corneal opacity and vascular keratitis P and F1 males) and an increased incidence of pelvic dilation of the kidney (F0 and F1 males and F1 females) **Reproductive** NOAEL = 43.65/52.7, mg/kg/day (M/F) LOAEL = 435.5/534 mg/kg/day (M/F) based upon changes in sperm parameters, and a decrease procoital interval **Offspring** NOAEL = 2.15/2.65 mg/kg/day (M/F) LOAEL = 43.65/52.7 mg/kg/day (M/F) based upon decreased absolute body weights and body weight gains, and an increased incidence of litters with vascular keratitis in the F1 and F2 generations
870.4100b	Chronic toxicity (dog)	47841977 (2012) acceptable/guideline 0, 2.5, 25, and 125 mg/kg/day [M/F]	NOAEL was not observed. LOAEL = 2.5 mg/kg/day based upon an increased incidence of chromatolysis and swelling of selected neurons in the dorsal root ganglia and degeneration of nerve fibres in the spinal nerve roots in both sexes.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4200	Chronic/Carcinogenicity (rat)	47841985 (2012) acceptable/guideline 0, 5, 500, 2500, and 5000 ppm (0, 0.32/0.39, 32.6/41.6, 166/204 and 335/404 mg/kg/day [M/F])	NOAEL was not established LOAEL = 0.28/0.35 mg/kg/day (M/F) based on a dose dependent increase in the incidence of opaque eyes and corneal damage in both sexes compared to controls, an increased incidence of thyroid follicular hyperplasia in males, and an increased incidence of chronic progressive nephropathy in the kidneys of males.**Evidence of carcinogenicity (an increased occurrence of ocular squamous cell carcinomas and papillomas at 500, 2500, and 5000 ppm.)**
870.4300	Carcinogenicity (mouse)	47841987 (2012) acceptable/guideline 0, 70, 1700, 7000 ppm (0, 8.7 / 9.2, 233 / 242, 940 / 1027 mg/kg/day [M/F])	NOAEL = 1700 ppm (233 mg/kg/day [F])/ 7000 ppm (233 mg/kg/day [M]) LOAEL = 7000 ppm (940 mg/kg/day [F])= based upon decreased absolute body weights in females. The LOAEL for males was not established.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5100	Bacterial Mutation Assay In S.typhimurium And E.coli	47841979 (2007) acceptable/guideline Non-activated conditions: 5000, 2500, 1000, 500, 200 and 100 µg/plate Activated conditions: 5000, 2500, 1000, 500, 200 and 100 µg/plate	It is concluded that, under the conditions of this assay, bicyclopyrone gave a negative, i.e. non-mutagenic, response in*S.typhimurium* strains TA1535, TA1537, TA98 and TA100 and *E.coli* strainsWP2 (pKM101) and WP2*urvA* (pKM101) in both the presence and absence of S9 -mix, and in strain TA1535 in the presence of S9 -mix.
870.5100	Salmonella typhimurium and Escherichia coli Reverse Mutation Assay	47841980 (2010) acceptable/guideline Nonactivated conditions: 5000, 2500, 1000, 333, 100, 33 µg/plate Activated conditions: 5000, 2500, 1000, 333, 100, 33 µg/plate	During the described mutagenicity test and under the experimental conditions reported, bicyclopyrone did not induce gene mutations by base pair changes or frameshifts in the genome of the strains used. Bicyclopyrone is considered to be non-mutagenic in the Salmonella typhimurium and Escherichia coli reverse mutation assay.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5300	*In Vitro* Mammalian Cell Gene Mutation Test	47841981(1997) acceptable/guideline 0, 3994, 2995, 1997, 1497, 998, 499, 250 and 125µg/mL (± S9)	It is concluded that, under the conditions of this assay, bicyclopyrone is not mutagenic in L5178Y TK+/- cells treated *in vitro* in either the presence or absence of S9-mix.
870.5395	Micronucleus Assay in Bone Marrow Cells of the Rat	47841984 (2008) acceptable/guideline 24 hr interval: 500, 1000, and 2000 mg/kg b.w. 48 hr interval: 2000 mg/kg b.w.	In conclusion, it can be stated that under the experimental conditions reported, the test substance did not induce micronuclei as determined by the micronucleus test with bone marrow cells of the rat. Therefore, bicyclopyrone is considered to be non-clastogenic in this micronucleus assay.
870.5550	*In Vivo* Rat Liver Unscheduled DNA Synthesis Assay	47841983 (2007) acceptable/guideline 2000 mg/kg [M]	Under the conditions of test, bicyclopyrone did not induce DNA repair, as measured by unscheduled DNA synthesis, in the rat liver *in vivo.*

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.6200a	Acute neurotoxicity screening battery (rats)	4782002 (2012) acceptable/guideline 0, 20, 200, 2000 mg/kg [M/F]	Neurotoxicity NOAEL= 2000 mg/kg. Neurotoxicity LOAEL was not observed. Systemic NOAEL= 2000 mg/kg Systemic LOAEL was not observed.
870.6200b	28- day preliminary Subchronic neurotoxicity screening battery (rats)	47842140 (2012) acceptable/non-guideline 0, 500, 2500 and 5000 ppm ppm M: 0, 50, 240 and 471 mg/kg/day F: 0, 53, 259 and 505 mg/kg/day	Systemic NOAEL = 5000 ppm (471/505 mg/kg/day [M/F]) Systemic LOAEL was not observed Neurotoxic NOAEL = 5000 ppm (471/505 mg/kg/day [M/F]) Neurotoxic LOAEL was not observed

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.6200b	90-day Subchronic neurotoxicity screening battery (rats)	4782004 (2012) acceptable/guideline 0, 50, 500, 5000 ppm (0, 4/4, 35/42, and 336/415 mg/kg/day [M/F])	Neurotoxicity NOAEL was not observed. Neurotoxicity LOAEL = 50 ppm (4 mg/kg/day) based upon a statistically significant treatment related decrease in the absolute brain weights of males. Systemic NOAEL was not observed. Systemic LOAEL is 50 ppm (4 mg/kg/day) based upon an increased incidence of unilateral keratitis in the eyes of males.

870.7465	Metabolism and pharmacokinetics (rat)	47841961, 47841962, 47841963, 47841964, 47841965, 47842110 (2010) acceptable/guideline 0, 2, 200 mg/kg	Using bile-cannulation experiments, absorption from the GI-tract was estimated to be 83% - 87% for the low dose in both sexes. The estimated absorption for the high dose was 86% - 90% for both sexes. Maximum mean plasma concentrations (Cmax) were reached in both male and female rats within 1.3-2.3 hours (Tmax), indicating rapid absorption kinetics for the low dose group. Cmax values increased proportionally with dose suggesting nearly linear absorption. The levels of radioactivity in plasma declined rapidly in a biphasic pattern. The mean plasma clearance half-life values of the first phase (α-phase) were estimated at 2.4-2.7 hours at 2 mg/kg bw in both sexes, and were noted to increase modestly at 200 mg/kg bw to 3.2 hours in males but not in females. At the low dose, it was not possible to calculate a half-life value for the second (β-phase) because the majority of samples were at or below the limit of detection. At 200 mg/kg bw, the mean plasma β half-life values were estimated at 12.5 and 68.6 hours in males and females respectively. The highest levels of radioactivity were found in the liver and kidney. This pattern of tissue accumulation was independent of time, frequency of dosing and amount of dosing. All other tissues were approaching or below the limit of detection. Radioactivity in the carcass accounted for <0.7% of the administered dose. At both dose levels, the major radioactive component in the urine of non-cannulated rats

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
			was parent compound, accounting for *ca* 40% and 80% of the dose in males and females respectively, indicating more metabolism in males. In bile duct cannulated rats, the metabolite profile in urine was similar to that obtained from intact rats. The metabolite profile obtained from rats administered multiple low doses of bicyclopyrone was similar to that obtained from the equivalent single dose. There were no significant differences in the patterns of excretion between the sexes. For the low dose, the major routes of excretion were
870.7600	*In vivo* dermal absorption (rat)	47842239 (2009) acceptable/guideline 0, 0.05, 0.2, and 20 mg/kg bicyclopyrone	Following a 6 hour dermal exposure to bicyclopyrone soluble liquid (SL) formulation concentrate (A16003E) and to 1/100 and 1/400 spray strength dilutions thereof, most of the applied dose was readily removed from the skin surface by mild skin washing. In all dose groups residues remained in the skin after washing and thereafter declined in concentration over the 120 hour assessment period. Absorption of bicyclopyrone over a time course of 6 hours accounted for 23.49%, 21.71% and 24.01% of the 3 respective applied doses.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7800	Immunotoxicity (mice)	47842008 (2012) acceptable/guideline 0, 50, 500, 5000 ppm (0, 10.6, 107.2 and 1192 mg/kg/day [F])	Immunotoxicity NOAEL = 5000 ppm Immunotoxicity LOAEL was not observed. Systemic NOAEL = 5000 ppm Systemic LOAEL was not observed.

TABLE 4. Metabolite profile in excreta of rats dosed with C^{14}-labeled Bicyclopyrone (NOA449280)[a]
[Metabolites must be given as percent of dose. *If possible the reviewer should perform the necessary conversions, include Total identified, Total unidentified, Total accounted for, Total lost or unaccounted (see below)]*

Dose	**Percent of administered dose**					
	Oral dose		**Treatment 2 (If Applicable)**		**Treatment 3 (If Applicable)**	
Compound	**Male**	**Female (If Applicable)**	**Male**	**Female (If Applicable)**	**Male**	**Female (If Applicable)**
Parent	43.7	84.8				
CSAA915194	16.2	2.2				
CSCD6758164, CSCD677306, CSCD675162 and CSCD677693	28.6	6.8				

TABLE 4. Metabolite profile in excreta of rats dosed with C^{14}-labeled Bicyclopyrone (NOA449280)[a]
[Metabolites must be given as percent of dose. *If possible the reviewer should perform the necessary conversions, include Total identified, Total unidentified, Total accounted for, Total lost or unaccounted (see below)]*

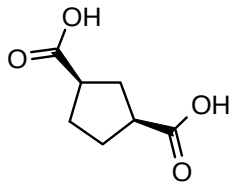
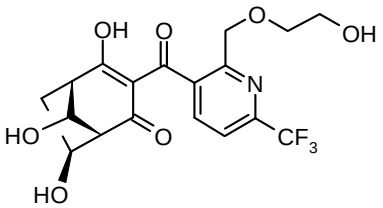
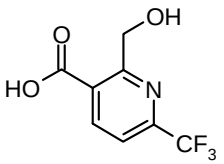
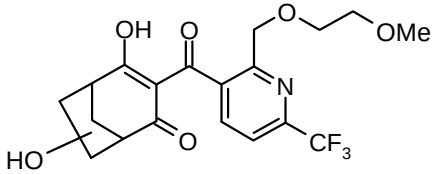
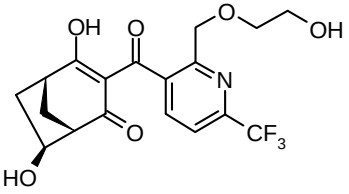
Dose	Percent of administered dose					
	Oral dose		Treatment 2 (If Applicable)		Treatment 3 (If Applicable)	
Compound	Male	Female (If Applicable)	Male	Female (If Applicable)	Male	Female (If Applicable)
(Males Only)						
Total identified	5	3				
Unidentified metabolite X	0.8	0.91				
Unidentified metabolite Y						
Unidentified at origin or at some band						
Total unidentif.	0.8	0.91				
Total accounted for [b]	89.7	93.2				
Lost/unaccounted for [c]	10.3	6.8				
Total	100	100	100	100	100	100

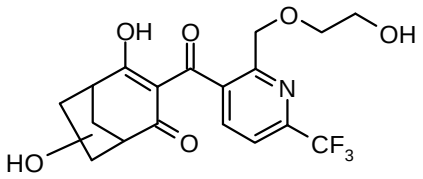
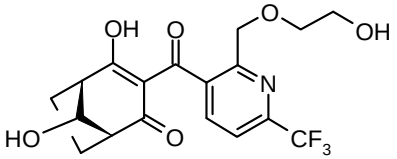
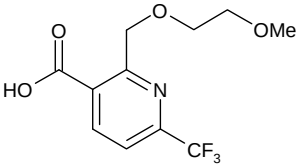
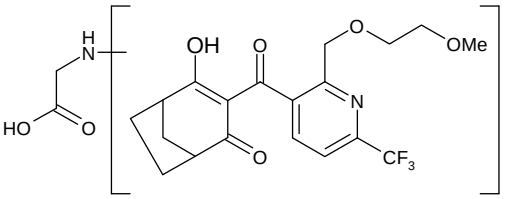
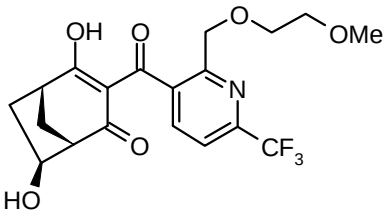
[a] Data obtained from pages *(insert page 34-44)* in the study report (MRID #47841962).
[b] Total accounted for = (Total identified) + (Total unidentified)
[c] 100 - (Total accounted for)

1.1 Metabolite Profiling And Identification

Pooled samples of urine, faeces, bile, cage wash, plasma and liver were analysed by HPLC and LC/MS to determine the metabolite profile. Metabolites were identified by radio-HPLC-MS using a combination of HPLC comparative chromatography with authentic reference standards, accurate mass measurement and MS^n fragmentation. Minor metabolites were tentatively identified and assigned a

proposed chemical structure based on mass spectroscopy data. HPLC retention times for standards are detailed in APPENDIX 3. Full details are presented in the Mass Spectrometry report in APPENDIX 4. The following metabolites of NOA449280 were identified in the rat**:**

Metabolite	**Structure**
CSAA589691	
CSCD677692	
CSAA806573	
Hydroxy NOA449280	
CSCD675162	

Metabolite	**Structure**
Desmethyl monohydroxy NOA449280 (2 isomers)	
CSCD677693	
SYN503780	
NOA449280 (Glycine)	
CSCD675164	

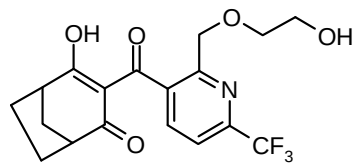
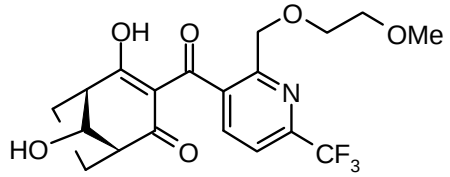
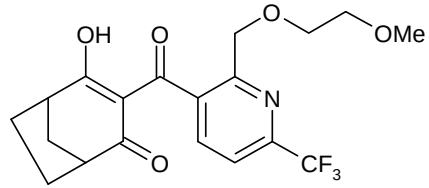
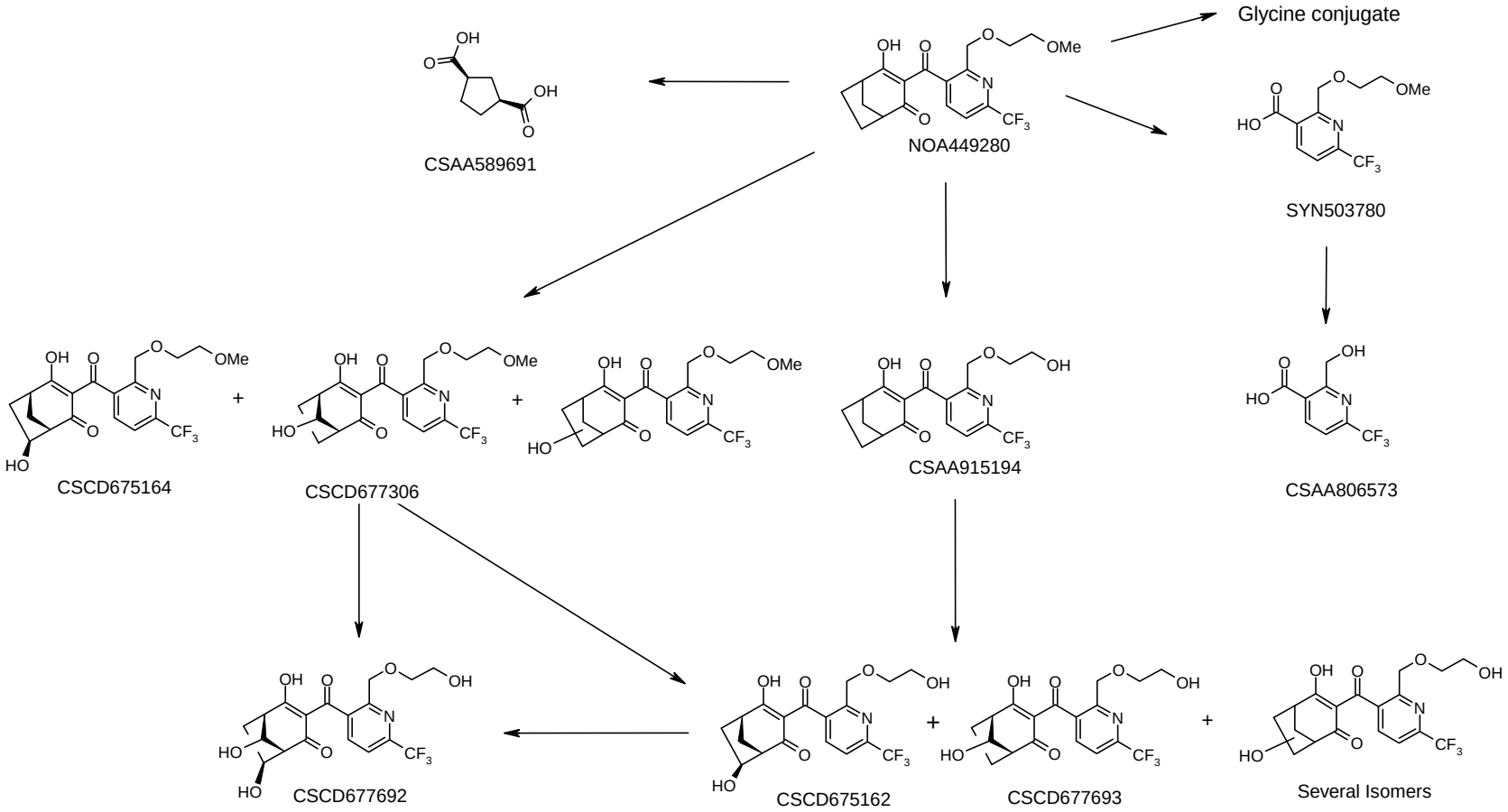
Metabolite	**Structure**
CSAA915194	
CSCD677306	
NOA449280	

FIGURE 1 Proposed Metabolic Pathway of NOA449280 in the Rat



CSAA589691 was detected by MS but could not be quantified as this metabolite was derived from a part of the NOA449280 molecule that did not contain ^{14}C radiolabelling

Other Considerations

Although this information does not need to be included in the briefing materials, the risk assessment teams should be prepared to answer the following questions during the meeting.

- Residue analytical methodology, including multiresidue method testing results
- Results of literature searches
- Results of any SAR/QSAR Evaluations (e.g., evaluations from Cancer Assessment Review Committee (CARC))